DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

466 Fernandez Juncos Avenue
Puerta De Tierra
San Juan, Puerto Rico 00901-3223

September 18, 2001

WARNING LETTER
SJN-01-19

CERTIFIED MAIL
Return Receipt Requested

Mr. Fred Hassan
President and Chief Executive Officer
Pharmacia & Upjohn
100 Route 206 North
Peapak, NJ 07097

Dear Mr. Hassan:

From April 3 through July 12 and again on July 30 through August 8, 2001, investigators from this office conducted an inspection of your human drug manufacturing facility Pharmacia & Upjohn Caribe, Inc. located at Hwy 2 km 60.0, Arecibo, PR 00612. Our investigators found the drug products manufactured by your firm to be adulterated within the meaning of Section 501 (a)(1) of the Federal Food, Drug and Cosmetic Act. In addition, our investigators found significant violations of the regulations covering the Current Good Manufacturing Practices for finished pharmaceuticals as defined by Title 21, Code of Federal Regulations, Part 210 & 211). These violations cause the drug products manufactured by your firm to be further adulterated within the meaning of Section 501 (a)(2)(B) of the Federal Food, Drug and Cosmetic Act.

The deficiencies found during the inspection, and reported on the lists of Inspectional Observations, FDA-483, presented at the conclusion of each of the inspections include the following:

Failure to control microbiological contamination in products not required to be sterile as required by 21 CFR 211.113. On several occasions, finished Glyburide tablets were released and distributed containing high counts of fungi including Penicillium spp., Aspergillus spp., Botryotrichum spp. and Paecilomyces spp. The investigators found that in 1995, [redacted] lots of Glyburide tablets were contaminated with fungi with counts as high as 320 colony-forming units (CFUs)/tablet. The contamination was traced to the [redacted] used to manufacture the finished product. In 1997, your firm again detected fungi contamination in [redacted] lots of Glyburide tablets with results as high as 140 CFUs/tab, again tracing the source of the contamination to the DCPH used to manufacture the lots. In 2000, your firm found [redacted]

lots of Glyburide tablets to be contaminated with fungi and another [redacted] lots in 2001. In each instance, the contamination was traced to the [redacted] used to manufacture the Glyburide tablets. All 51 lots listed above for released by your firm for commercial distribution.

Failure to perform adequate investigations into the cause of the contamination of the Glyburide tablets with fungus and to extend the investigations to other lots of Glyburide tablets that were manufactured with the same lot of [redacted] found to be contaminated with fungi as required by 21CFR 211.192.

Failure to appropriately sample and test components as required by 21 CFR 211.84. After [redacted], a component of Glyburide tablets, was found to contain large numbers of fungi in 1995, 1997 and 2000, your firm failed to take appropriate action by sampling ant testing the [redacted] in such a manner that the contamination, if present, would be detected. Subsequently, in 2001, a lot of [redacted] was received and used to manufacture Glyburide tablets and was latter determined to be contaminated with fungi at a level to numerous to count.

Failure to submit a NDA Field Alert Reports as required by 21 CFR 314.81. You did not submit any NDA Field Alert Reports to the SJN-DO district after you became aware that Glyburide tablets were contaminated with fungi described above.

We acknowledge receipt of your response dated July 27, 2001 to the FDA-483 dated July 12, 2001 and your response dated September 6, 2001 to the FDA-483 dated 7/12/01. Our evaluation of the response finds that, except for the items listed above, the proposed corrections will satisfactorily address the observations if adequately implemented.

Neither this letter nor the list of inspectional observations is meant to be an all-inclusive list of deviations at your facility. It is your responsibility to ensure that your facility is in compliance with the provisions of the Federal Food, Drug and Cosmetic Act and all applicable regulations and standards. Federal agencies are advised of the issuance of all Warning Letters about drugs so that they may take this information into account when considering the award of contracts.

Please notify the San Juan District office in writing, within 15 working days of receipt of this letter, of you response to the violations identified in this letter. Corrective actions addressed in your letter may be referenced in you response to this letter as appropriate. Failure to promptly correct these deviations may result in regulatory action, including seizure, injunction, and/or prosecution, without further notice.

Your reply should be sent to the Food and Drug Administration, San Juan District Office, 466 Fernandez Juncos Avenue, San Juan, PR, 00901-3223, Attention: Mary L. Mason, Compliance Officer.

Sincerely,

Mildred R. Barber
San Juan District Office

Cc:
Mr. Francisco Pascacio
Vice President & General Manager
Pharmacia & Upjohn
PO BOX 11307
Barceloneta, PR 00617-1307